REMARKS

Claims 18-19, 21, 23-24 and 26-28 stand objected to as containing non-elected subject matter. For the sake of clarity, Claims 18-19, 21, 23-24 and 26-28 have been canceled without prejudice and new Claims 33-44 have been entered. New Claim 33 generally tracks the language of now-canceled Claim 18, except the new claim is drawn to proteins of at least about 20 amino acids in length. Support for proteins of 20 amino acids may be found in the specification, for example, on page 43, lines 16-22. The remainder of the new claims substantially track the original claims. Accordingly, Applicants submit no new matter has been added.

Claims 18-19, 21, 23-24 and 26-28 stand rejected under 35 U.S.C.§101 and 35 U.S.C.§112, first paragraph. Applicants have reviewed the grounds for the rejections, but traverse for the reasons set forth below. Although the rejections are directed to now-canceled claims, Applicants' remarks below also relate to the corresponding new claims.

I. Rejections Under 35 U.S.C.§101

The Examiner has rejected Claims 18-19, 21, 23-24 and 26-28 under 35 U.S.C.§101 as lacking patentable utility. According to the Examiner, the specification fails to establish that the disclosed polynucleotide sequences encode an amino acid sequence, which is an IL-13 like protein as shown by structural and/or functional properties. The Examiner contends the recited SEQ ID NO(s) are simply computer-generated hypothesis and, further, the specification fails to show a single working example which establishes the polynucleotides of the instant invention encode a protein having IL-13 like activity as determined either by substantial sequence homology and/or functional assay of the protein. Moreover, a sequence comparison performed by the Examiner reveals the instant sequence has 68-69% similarity to human IL-13, which the Examiner considers to be a low percentage of similarity. Based on the low similarity with other IL-13 proteins and the perceived lack of demonstrated functional activity, the Examiner contends one skilled in the art would not readily attribute IL-13 activity to a protein encoded by the instant nucleic acid molecule. The Examiner concludes since no function can be ascribed to the claimed protein, the use asserted in the application is not supported and, therefore, the claimed protein lacks utility.

Applicants contend the specification adequately demonstrates sufficient utility for the claimed proteins, based on both sequence identity and functional activity, to satisfy 35 U.S.C. §101. First, Applicants direct the Examiner's attention to page 151 of the specification that

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states sequence alignments were performed using DNAsis, and further states PcaIL-13_{131} (SEQ ID NO 92) has 61.7% **identity** with the human IL-13 (huIL-13) protein. Applicants emphasize this comparison was not based on **similarity**, which allows for conservative amino acid substitutions at corresponding positions, but rather, was based on **identity**, which scores only exact matches between the two sequences and is therefore a more stringent measure of sequence homology. Applicants contend the level of identity between SEQ ID NO. 92 and the recognized huIL-13 protein is substantial enough to conclude that the proteins of the instant invention are members of the IL-13 family. In support, Applicants point to McKenzie et al. (PNAS, 90:3735-3739, 1993), which is of record, and which states two other recognized IL-13 proteins, namely huIL-13 and murine IL-13 (mIL-13), share a percentage identity of 58%, a degree of homology even lower than the homology taught in the present invention. Since these two other species of recognized IL-13 proteins share a percentage identity lower than that shared by huIL-13 and a disclosed caIL-13, it is reasonable to concludethese proteins are members of the IL-13 protein family based on sequence homology,.

Furthermore, a sequence comparison performed by the Applicants using NCBI BLASTP with default parameters (Exhibit A; submitted herewith), in which SEQ ID NO:92 was compared to the NCBI protein database showed that of the eleven proteins sharing significant homology with SEQ ID NO:92, all are recognized IL-13 proteins. The degree of homology between SEQ ID NO:92 and various IL-13 proteins ranges from 58%-71% identity. Outside of the IL-13 family, the protein with the next highest level of homology to SEQ ID NO:92 is the preprosperminogen protein of *Oryctolagus cuniculus* (rabbit), a totally unrelated protein with only 28% identity over a short region (52 amino acids) of the sequence. In this regard, Applicants direct the Examiner's attention to the USPTO's Revised Interim Utility Guidelines Training Materials, and in particular, Example 10. According to this Example, when a claimed sequence shows significant homology to a known family of proteins, and the next most homologous protein outside the family has a significantly lower homology and an unrelated function, then there is "no reason to doubt" the claimed protein has the function of the proteins in the family. Furthermore, although alignments were performed using SEQ ID NO 92, Applicants submit the results of the BLASTP comparison and the above referenced guidelines also apply to SEQ ID NOs 97, 100 and 105 since these amino acid sequences are overlapping with and present

within SEQ ID NO:92. Applicants therefore contend the stated homologies clearly place the claimed protein in the IL-13 family as taught by the USPTO guidelines.

Next, with regard to functional activity, Applicants direct the Examiner's attention to Example 6 in the specification that teaches a protein of the present invention possesses IL-13 activity. The Example demonstrates that when a recombinantly expressed protein, comprising SEQ ID NO 97, is added to TF-1 cells, the cells are induced to proliferate. While the Examiner has argued this activity can be found in several other proteins, Applicants maintain it is also a property of IL-13 proteins. Given Applicants have shown a protein with high degree of homology to known IL-13 proteins possesses functional activity of IL-13, Applicants contend they have described at least one utility that supports the asserted use of the protein.

Furthermore, it is well-recognized that only one credible utility is needed to satisfy the utility requirement of 35 U.S.C. §101. In this regard, Applicants further direct the Examiner's attention to page 26, lines 10-23, through page 27 lines 1-16 of the specification, where the use of proteins, or peptides, of the present invention to produce an immune response against these proteins is described. The Examiner's attention is also directed to page 97, line 12- 23, through page 99, lines 1-19, where these use of antibodies, produced by an immune response to proteins of the present invention, is disclosed.

In view of the foregoing, Applicants request that the rejections under 35 U.S.C.§101 be withdrawn.

II. Rejections Under 35 U.S.C.§112, First Paragraph

The Examiner has rejected Claims 18-19, 21, 23 and 26 under 35 U.S.C.§112, first paragraph as containing subject matter not described in such a way as to reasonably convey that the inventors had possession of the claimed invention at the time of filing. Specifically, the Examiner states the invention encompasses any and all variants of IL-13, while only disclosing the amino acid sequences of SEQ ID NO: 92, 97, 100 and 105. Further, the Examiner contends the genus of IL-13-like polypeptides would have widely divergent functional properties and the general knowledge in the art regarding IL-13 proteins does not provide any indication of how the structure of one allele is representative of other unknown sequences having concordant or discordant function. The Examiner maintains the common attributes of IL-13 proteins, other than the SEQ ID NOs as claimed, are not described and therefore concludes that one skilled in the art would not recognize the applicant was in possession of the invention at the time of filing.

Applicants contend adequate description of the attributes common to the claimed proteins can be found throughout the specification and in the claims. According to USPTO guidelines (Federal Register Vol. 66, No. 4), possession of an invention may be demonstrated, in part, by disclosure of complete or partial structure, functional characteristics coupled with a known or disclosed correlation between structure and function, or a combination of such characteristics.

First, with regard to disclosure of a complete or partial structure, the specification teaches specific amino acid sequences for canine IL-13. In addition, the structure of related members of the genus is defined by allelic variants or proteins having at least 70% identity to these specific sequences.

With regard to allelic variants, Applicants contend such variants do not encompass "any and all" sequence variations, but only those encompassed by the structural definition of allelic variants as taught in the specification. The Examiner's attention is directed to page 40, lines 4-20, of the specification where an allelic variant is defined as a gene that occurs at essentially the same locus, has a similar but not identical sequence, and encodes a protein having a similar activity as that of the protein encoded by the gene to which it is being compared. Therefore, the claimed allelic variants, by definition, must possess IL-13 activity.

With regard to new Claim 39 (formerly Claim 21), Applicants contend it is well known in the art that IL-13 proteins from different species may diverge in sequence by as much as 40% while still maintaining IL-13 activity, as described, for example, in McKenzie PNAS, 90:3735-3739,1993. Additional support for Applicants' position may be found in the attached BLASTP alignments (Exhibit A), provided to the Examiner herewith, and in the discussion above relating to utility. Based on the knowledge in the art, it is reasonable to conclude that molecules which share 70% structural identity are variant members of the same protein family.

Furthermore, Applicants contend that not "any or all" sequence variants are encompassed by the claims. The structural elements discussed in the previous paragraph must be coupled with the claimed function of eliciting an immune response against a canine IL-13 protein or having IL-13 activity. Accordingly, the claims are only directed to variant sequences having the claimed function. Because the claims couple a functional activity to the above structural limitations, Applicants submit the claims do not encompass proteins unrelated to canine Il-13, but instead encompass a well-defined set of molecules that couple structure with function sufficient to satisfy the USPTO guidelines.

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The Examiner has further rejected Claims 18-19, 21, 23-24 and 26-28 under 35 U.S.C.§112, first paragraph, as containing subject matter which was not described in such a way as to enable one skilled in the art to make and/or use the invention. The Examiner states the invention as claimed encompasses any and all variants of IL-13 from any and all animals. However, according to the Examiner "the specification at best discloses that E. coli produced canine pCaIL-13 recombinant protein stimulates the proliferation of TF-1 cells." The Examiner further states the art at the time of filing teaches that a number of cytokines will induce TF-1 cell proliferation and, therefore, it is unclear whether the isolated proteins, as claimed, have any IL-13 specific activity. Moreover, it is unclear whether any and all variants of the claimed SEQ ID NO(s) have the biological activity of IL-13. Additionally, the Examiner maintains the relationship between a protein's sequence and its tertiary structure is neither well understood or predictable and that amino acid substitutions present in IL-13 variants may adversely effect biological activity if the substituted amino acids are critical for folding and/or function of the molecule. Finally, the Examiner states the art at the time of filing teaches that IL-13 is involved in the regulation of Th2 responses, which according to the Examiner are complex and involve the interaction of many additional cytokines. Based on this complexity, the Examiner contends it is unclear how one of skill in the art would use the claimed SEQ ID NO(s) or its variants without undue experimentation. Therefore, in view of the lack of specific guidance and the need for excessive and undue experimentation, the Examiner concludes the invention is not enabled in scope with the claims.

First, Applicants reiterate the claims do not encompass " any and all" sequence variants and direct the Examiner's attention to the above arguments which explain that the claimed proteins are limited to those with a defined structure **and** that possess either IL-13 activity or the ability to stimulate an immune response against canine IL-13. Applicants contend that by using the teaching of the specification, one of skill in the art would be able to determine if a particular isolated protein has such activity and therefore falls within the scope of the claims. With regard to the Examiner's objection that the assay for IL-13 activity taught in the specification is not specific for IL-13 and may be used to measure the activity of several different cytokines, Applicants contend the fact the TF-1 cell proliferation assay taught in the specification can be used to measure the activity of different cytokines is not germane to enablement of the current invention. Given the similar roles of various cytokines in the immune system, it is not surprising

that a number of them share the ability to stimulate T-cell proliferation. To satisfy the enablement requirement with regard to the present invention, the specification must merely teach how one skilled in the art could determine whether a particular isolated protein demonstrates activity representative of activity inherent in functional IL-13. Applicants submit that the TF-1 cell proliferation assay satisfies this criteria, and further, that the presence of this activity, coupled with the recited structural limitations ensure that proteins which fall within the scope of the claims are within the family of IL-13 proteins. The fact other cytokines can also cause TF-1 cell proliferation does not invalidate this assay for its stated purpose since other cytokines would not have the structural similarity to be encompassed by the claims.

Additionally, Applicants contend a positive correlation has been shown to exist between TF-1 cell proliferation and several other assays used to measure IL-13 activity. Specifically, mutations in IL-13 that increase the protein's ability to stimulate TF-1 cell proliferation likewise affect the protein's activity in other assays used to measure IL-13 activity, including plasmacytoma B9 cell proliferation, monocyte CD14 down-regulation and STAT 6 activation in THP-1 cells, as shown in Oshima et al., J. Biol. Chem. 2000 May 12; 275(19): 14375-14380, (Exhibit B) a copy of which is submitted herewith. The fact that all of these assays respond in a similar manner to mutated forms of IL-13 suggests they are all measuring the same fundamental activity. Based on this result, Applicants contend the TF-1 cell proliferation assay is a reasonable method for measuring IL-13 activity.

Moreover, Applicants assert the ability to stimulate TF-1 cell proliferation was well-accepted in the art as a means to measure IL-13 activity at the time the application was filed. See, e.g., McKenzie et al., Proc. Natl. Acad. Sci. U.S.A. 1993 April 15; 90(8):3735-3739; and Lakkis et al., Biochem Biophys Res Commun 1997 June 27; 235(3):529-532 (Exhibit C). A copy of the Lakkis paper is submitted herewith. In view of the arguments and above cited references, Applicants submit that TF-1 cell proliferation is an appropriate means of measuring IL-13 activity.

With regard to proteins having 30% sequence variation from the amino acid sequences of SEQ ID NOs 92, 92, 100 and 105 (new Claim 39; formerly Claim 21), Applicants have amended claims encompassing such protein Claim 39 to include a functional activity for the protein variants. Applicants contend it is well within the ability of one of skill in the art to measure this activity using the guidance provided in the specification.

Finally, Applicants contend one of skill in the art would be able to use the instant invention without the need for undue experimentation. In making a determination of undue experimentation, several factors must be considered including the state of the art, the relative skill of those in the art, the amount of guidance present in the specification as well as the quantity of experimentation necessary to use the invention. The specification teaches proteins of the instant invention may be used to regulate an immune response, examples of such regulation can be found on page 26, lines 10-14 of the specification. As disclosed in the specification, the claimed proteins can be used directly for this purpose or they can be used to isolate an inhibitor which can be used to regulate the immune response. Applicants contend the level of knowledge and skill in the art at the time of filing was such that one of skill in the art could use IL-13 to regulate the immune response in a relatively predictable manner. In support, the Examiner's attention is directed to de Vries, J., J. Allergy Clin. Immunol. 1998; 102:165-169 (Exhibit D; copy submitted herewith), which reviews the known effects and roles of IL-13 in the inflammatory process. Furthermore, Applicants contend adequate guidance on the general use of IL-13 and its inhibitors as immunomodulators can be found in the specification, for example page 23, lines 4-10 of the specification, which defines regulation of an immune response, and also page 26, lines 10-14, which illustrates exemplary effects of IL-13. Moreover, examples of specific methods of administration are taught in the specification, for example on page 99, lines 20-23, through page 104, lines 1 and 20, as are preferred dosages, for example on page 104, lines 7-20. Applicants assert more specific methods of using IL-13 or its inhibitors as immunomodulators were known to those skilled in the art; see for example Muchamuel et al., J. Immunol., 1997, 158:2898-2903 (Exhibit E), a copy of which has been included for the Examiner's convenience. Applicants maintain that one of skill in the art could apply the teaching of the specification, along with the general knowledge available in the field, to use the present invention for the regulation an immune response, as described in the specification. While Applicants acknowledge some experimentation might be necessary to achieve optimal results, such experimentation would not be undue. At most, the use of the functionally active IL-13 molecules covered by the claims would require testing and optimization of dosages and dosing schedules in target animals to achieve the desired immunoregulatory effect. Applicants submit that such testing is routine and can be easily accomplished by those skilled in the art. As stated by the court in *Amgen v Chugai*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed Cir. 1991), "That

some testing is necessary does not constitute a lack of enablement." Additionally, the court in *W.L. Gore & Assoc. v. Garlock*, 721 F.2d 1540, 220 USPQ 303 (Fed Cir. 1983), ruled that some trial and error is permissible and stated, "...a patent is not invalid because of a need for experimentation." Additionally, the court in *In re Wands*, 858 F.2d 731, USPQ2d 1400 (Fed. Cir. 1988), held that a considerable amount of experimentation is permissible if it is merely routine. Applicants submit that the testing and optimization of the claimed proteins amount to routine screening well within the abilities of one skilled in the art. Therefore, in view of the preceding amendments and arguments, Applicants request the claim rejections under 35 U.S.C.§112, first paragraph be withdrawn.

CONCLUSION

In view of the above amendments and remarks, Applicants request withdrawal of all rejections of the claims and solicit allowance of all pending claims. Any questions regarding Applicants' position should be directed to Theresa Brown at the telephone number shown below.

Respectfully submitted,

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VERSION WITH MARKINGS SHOWING CHANGES

Claims 18-19, 21, 23-24 and 26-28 have been canceled.

The following new claims have been added:

33. (New) An isolated protein selected from the group consisting of:

(a) an isolated protein of at least about 20 amino acids in length, wherein said protein is encoded by a nucleic acid molecule, wherein said nucleic acid molecule has an at least 60 contiguous nucleotide region identical in sequence to a 60 contiguous nucleotide region of a nucleic acid sequence selected from the group consisting of SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:94, SEQ ID NO:96, SEQ ID NO:99, SEQ ID NO:102, and SEQ ID NO:104; and

(b) an isolated protein of at least about 20 amino acids in length, wherein said protein has an at least 20 contiguous amino acid region identical in sequence to a 20 contiguous amino acid region selected from the group consisting of SEQ ID NO:92, SEQ ID NO:97, SEQ ID NO:100, and SEQ ID NO:105,

wherein said isolated protein of (a) or (b) elicits an immune response against a canine IL-13 protein or has IL-13 activity.

34. (New) The isolated protein of Claim 33, wherein said protein is selected from the group consisting of:

(a) a protein having an amino acid sequence selected from the group consisting of SEQ ID NO:92, SEQ ID NO:97, SEQ ID NO:100, and SEQ ID NO:105; and

(b) a protein encoded by an allelic variant of a nucleic acid molecule encoding a protein having an amino acid sequence selected from the group consisting of SEQ ID NO:92, SEQ ID NO:97, SEQ ID NO:100, and SEQ ID NO:105.

35. (New) The isolated protein of Claim 34, wherein the protein has the amino acid sequence of SEQ ID NO:92.

36. (New) The isolated protein of Claim 34, wherein the protein has the amino acid sequence of SEQ ID NO:97.

37. (New) The isolated protein of Claim 34, wherein the protein has the amino acid sequence of SEQ ID NO:100.

38. (New) The isolated protein of Claim 34, wherein the protein has the amino acid sequence of SEQ ID NO:105.

39. (New) An isolated protein having an amino acid sequence that is at least about 70 percent identical to an amino acid sequence selected from the group consisting of SEQ ID NO:92, SEQ ID NO:97, SEQ ID NO:100, and SEQ ID NO:105, wherein said protein elicits an immune response against a canine IL-13 protein or has IL-13 activity.

40. (New) A therapeutic composition comprising a therapeutic compound selected from the group consisting of:

(a) the isolated protein of Claim 33;

(b) a mimetope of said protein of (a);

(c) a multimeric form of said protein of (a);

(d) an antibody that selectively binds to said protein of (a); and

(e) an inhibitor of a immunoregulatory protein activity identified by its ability to inhibit the activity of said protein of (a).

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41. (New) The composition of Claim 40, wherein said composition further comprises a component selected from the group consisting of an excipient, an adjuvant and a carrier.

42. (New) A method to regulate an immune response in an animal comprising administering to the animal the therapeutic composition of Claim 40.

43. (New) The method of Claim 42, wherein said animal is selected from the group consisting of canids.

44. (New) The method of Claim 42, wherein said composition further comprises a component selected from the group consisting of an excipient, an adjuvant and a carrier.

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